Negative Symptoms and Regional Cerebral Blood Flow in Patients with Schizophrenia: A Single Photon Emission Computed Tomography Study

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There have been few functional imaging studies of negative symptoms in schizophrenia during the resting state, particularly in Asian patients with schizophrenia. The aim of this study was to evaluate the relationship between regional cerebral flood flow (rCBF) and negative symptoms, and to discuss the association between severity and subgroups of negative symptoms and rCBF. Sixteen patients with chronic schizophrenia were evaluated for negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS), and brain single photon emission computed tomography (SPECT) imaging to assess rCBF during the resting state. Results were assessed using Spearman's correlation analysis. Total SANS scores were significantly negatively correlated with bilateral hypofrontality, especially in the left orbital frontal and bilateral superior frontal areas. Subscores for attention were significantly negatively correlated with the left lower frontal-temporal area and the right cerebellum. Subscores for anhedonia had a negative correlation with the right hemisphere. Subscores for affect were negatively correlated with rCBF in the bilateral prefrontal and bilateral superior frontal areas. There were no associations between rCBF and SANS in alogia and avolition. These results support the notion that frontal lobe dysfunction in schizophrenia is associated with negative symptoms. The left anterior hemisphere may play an important role in attention deficit. These relationships between negative symptoms and neuroanatomy require further clarification.

Key Words: negative symptoms, schizophrenia, regional cerebral blood flow, Scale for the Assessment of Negative Symptoms, SANS
(*Kaohsiung J Med Sci* 2003;19:464–9)

Functional image research regarding the difference in regional cerebral blood flow (rCBF) between schizophrenics and healthy people has been ongoing for more than two decades. Hypofrontality has been found in 50% of resting-state studies, but more often in activation paradigms [1]. There have been few studies regarding the association between rCBF and negative symptoms on subscores in the resting state, particularly in Asian patients with schizophrenia, and the results are not consistent [2,3]. Interesting areas such as the frontal lobe [3–5] and the basal ganglia [2] have been mentioned, and more severe negative symptoms are usually found with more hypofrontality [2]. The aim of this study was to evaluate the relationship between rCBF and negative symptoms in the resting state, and to discuss the association between severity and

Received: June 19, 2002 Accepted: June 25, 2003
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subgroups of negative symptoms and rCBF in Chinese patients.

Materials and Methods

Subjects and clinical assessments

Patients with schizophrenia, based on DSM-III-R criteria, were recruited to the study. Exclusion criteria were a history of medical or neurologic diseases, tardive dyskinesia, a history of alcohol or substance dependence, head injury, electroconvulsive therapy, and the use of lithium treatment during the months prior to assessment.

All patients' clinical negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) 3 days before single photon emission computed tomography (SPECT). SANS comprises five subscores: affective flattening or blunting, alogia, avolition or apathy, anhedonia or asociality, and lack of attention [6,7].

Brain SPECT imaging

Each subject underwent SPECT scans. A venous line was inserted into the antecubital vein of the non-dominant arm to inject tracer (925 MBq, 25 mCi, of technetium-99m hexamethylpropylene amine oxime [^{99m}Tc-HMPAO]) 30 minutes before the study while patients kept their eyes open in a quiet environment. The triple-headed rotating gamma camera (MultiSPECT-3, Siemens, Hoffman Estates, Illinois, USA) used for imaging had ultra high resolution fan-beam collimators, which yield an image resolution of approximately 8.5 mm full width half-maximum (FWHM). SPECT data were acquired in a circular 360° rotation, with 120 steps of 30 seconds per step, in a 128 × 128 × 16 matrix. The data were then processed by filtered back projection with Butterworth and Ramp filters to reconstruct the transverse images. Reconstructed transverse images were aligned parallel to the canthomeatal (CM) line. The slice thickness of each transverse image was 2.89 mm.

Semi-quantitative analysis of brain SPECT images

A total of six transverse images, at 10 pixels, 14 pixels, 18 pixels, 22 pixels, 26 pixels, and 30 pixels above the CM line, were selected for analysis of the cortical regions of interest (ROIs) using a reference system method [8].

Cortical ROIs were defined automatically. The outer cortical border was demarcated by a threshold value, 50% of the maximal counts of the section. The inner cortical border was 8 pixels (23.18 mm) radically inward from the outer cortical border. The angular areas on each transverse image were divided equally into 30° sectors starting at the 12 o'clock position. As a result, there were 12 cortical ROIs on each transverse image. These ROIs were labeled clockwise and corresponded approximately to the anatomic regions of the brain. For example, cortical ROI S_1•2 (section 1, sector 2) and cortical ROI S_3•7 (section 3, sector 7) represent the left frontal and right occipital areas, respectively (Figure). ROIs at the thalamic, basal ganglion, and occipital levels were drawn manually by a senior nuclear medicine specialist. The mean count density of ROIs (representing the degree of tracer uptake in the region) was a marker of relative rCBF. In this study, rCBF in each ROI was normalized using the occipital region as the reference (ratio between one ROI and the mean for the occipital region) because the primary visual area was not hypothesized to be involved in negative symptoms and was included as a control region.

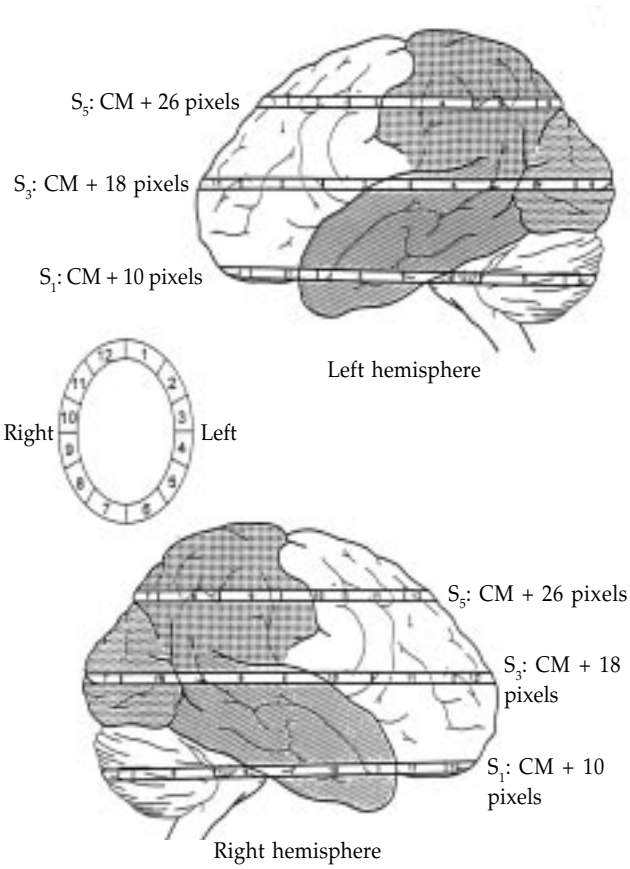

Figure. *Individual cortical regions of interest (ROIs) created by subdividing the cortical annulus into equal angular sectors (30°) approximately corresponding to the brain lobar structures as shown. For example, brain section 1 (S_1) is cut at 10 pixels above the canthomeatal (CM) line. Sector 6 of brain section 1 (S_1•6) is the left cerebellum. Brain section 3 (S_3) is cut at 18 pixels above the CM line. Sector 7 of brain section 3 (S_3•7) is the right occipital lobe. 1 pixel = 2.9 mm.*

Statistical analysis

Spearman's correlation analysis of non-parametric tests was used to assess the relationship between SANS subgroup scores and ROI. Since advanced age is reported to be associated with declining rCBF [9,10], the age effect was controlled for in the correlation analysis between rCBF and SANS scores. The Mann-Whitney test was used for continuous variables. Statistical calculations were carried out using SPSS/PC+V3.1 (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was considered a statistically significant correlation.

RESULTS

Of 16 patients, nine were men and seven were women. Their mean age was 33.29 ± 6.38 years (range, 25–50 years), the mean duration of illness was 10.35 ± 5.33 years, and the mean time in education was 12.44 ± 3.31 years. The mean dose of antipsychotic was equivalent to 407 ± 207 mg chlorpromazine; dosages were kept consistent during examination to avoid any latent interference in the study. Detailed data are shown in Table 1.

During the resting state, there was no association between rCBF and age, education level, age at onset of illness, duration of illness, or chlorpromazine-equivalent dose. There was no statistical difference in SANS scores by gender. After controlling for age effects, the total SANS score was significantly correlated with rCBF in the bilateral frontal region, especially in the left orbital frontal (S_2•1, r = –0.54; S_2•2, r = –0.57) and bilateral superior frontal areas (S_5•12, r = –0.59; S_5•2, r = –0.50; S_6•11, r = –0.54; S_6•1, r = –0.58; S_6•2, r = –0.51) (Table 2). The severity of negative symptoms was associated with a decrease in bilateral frontal cerebral blood flow in patients with schizophrenia.

SANS attention subscores were significantly negatively correlated with rCBF in the left lower frontal-temporal area (S_1•1, r = –0.54; S_1•2, r = –0.59; S_1•3, r = –0.56; S_1•4, r = –0.67) and the right cerebellum (S_1•8, r = –0.53) (Table 2). Anhedonia scores were significantly negatively correlated with rCBF in the right hemisphere, dispersed over the frontal (S_5•12, r = –0.53), temporal (S_2•10, r = –0.50), parietal (S_6•8, r = –0.56), and occipital areas (S_5•7, r = –0.69). In addition, affect subscores were significantly negatively correlated with rCBF in the bilateral prefrontal areas (S_2•1, r = –0.52; S_3•12, r = –0.50; S_4•1, r = –0.55) and bilateral superior frontal areas (S_5•1, r = –0.51; S_5•2, r = –0.63; S_5•12, r = –0.58; S_6•1, r = –0.59; S_6•2, r = –0.60; S_6•11, r = –0.54). There were no associations between rCBF and SANS alogia and avolition subscores.

DISCUSSION

Decreased frontal rCBF is associated with negative symptoms and more prominent negative symptoms are related to greater decreases in frontal rCBF [2]. However, inconsistent rCBF findings of frontal activities in schizophrenia during the resting state have been reported

Table 1. Demographic data of 16 patients with schizophrenia

Age (yrs)	Sex	Illness duration (yr)	Education (yr)	Medication* (mg)
35	M	17	12	600
35	M	8	9	400
35	F	10	12	100
34	M	16	12	367
32	M	7	12	400
40	F	13	12	365
28	F	10	12	1,060
34	F	16	12	390
30	M	8	14	400
22	F	4	12	1,000
25	M	6	12	610
35	M	9	16	250
36	M	10	9	164
46	F	23	6	250
26	F	4	12	360
44	M	12	22	160

*Chlorpromazine-equivalent dose.

Table 2. Correlation between regional cerebral blood flow (rCBF) and Scale for the Assessment of Negative Symptoms (SANS) scores

Brain region	Imaging slice*	Affect†	Anhedonia†	Attention†	Total score†
Right cerebellum	S_1 • 8	0.36	0.21	–0.53‡	0.10
Left frontal (orbital frontal)	S_1 • 1	0.16	–0.05	–0.54‡	–0.14
	S_1 • 2	0.18	0.10	–0.59‡	–0.05
Left temporal (middle inferior)	S_1 • 3	0.30	0.40	–0.56‡	0.16
	S_1 • 4	0.39	0.45	–0.67§	0.13
Right superior–middle temporal	S_2 • 10	–0.37	–0.50‡	0.14	–0.38
Left frontal (prefrontal)	S_2 • 1	–0.52‡	–0.49	–0.29	–0.54‡
	S_2 • 2	–0.47	–0.41	–0.37	–0.57‡
Right frontal (prefrontal)	S_3 • 12	–0.50‡	–0.46	–0.13	–0.47
Left frontal (prefrontal)	S_4 • 1	–0.55‡	–0.38	–0.07	–0.45
Right frontal (prefrontal)	S_5 • 12	–0.58‡	–0.53‡	–0.20	–0.59‡
Right occipital	S_5 • 7	–0.35	–0.69§	0.18	–0.40
Left frontal (prefrontal)	S_5 • 1	–0.51‡	–0.44	–0.17	–0.48
Left frontal (frontal eye field to premotor)	S_5 • 2	–0.63‡	–0.45	–0.05	–0.50‡
Right frontal (supplementary–premotor)	S_6 • 11	–0.54‡	–0.43	–0.28	–0.54‡
Right parietal	S_6 • 8	–0.50	–0.56‡	0.02	–0.43
Left frontal (prefrontal)	S_6 • 1	–0.59‡	–0.49	–0.22	–0.58‡
Left frontal (supplementary–premotor)	S_6 • 2	–0.60‡	–0.42	–0.18	–0.51‡

*See Figure; †after controlling for age effects; ‡$p < 0.05$; §$p < 0.01$.

since 1948 [3]. Liddle et al showed hypofrontality in patients with schizophrenia in a large cross-sectional study of 30 chronic schizophrenics [4]. Suzuki et al demonstrated that the negative symptoms in 39 schizophrenics were related to left frontal lobe dysfunction during the resting period [5]. Yuasa et al's studies of 26 medicated schizophrenia patients suggested psychomotor poverty correlated with decreased rCBF in the bilateral superior frontal areas, and increased rCBF in the left thalamus and right basal ganglia [11]. These studies revealed that the severity of negative symptoms was associated with hypofrontality. Our findings also support a decline in rCBF in the frontal areas during the resting state in schizophrenics with more negative symptoms.

Zemishlany et al investigated nine unmedicated schizophrenia patients at rest and during the continuous performance test (CPT) [12]. They found no association between rCBF and severity of negative symptoms during the resting state, but the severity of negative symptoms was associated with lower frontal activation during CPT and with higher posterior activation. This conclusion was supported by Erkwoh et al's studies of 24 never-treated actively psychotic schizophrenic patients [13], which showed that negative symptoms have no linkage to hypofrontality, either before or after treatment. These inconsistencies might be due to several reasons. First, small samples of patients mean that factors such as chronicity, severity of negative symptoms, level of functioning, and drug type and dosage vary across studies. Second, the definition of the resting state (eyes open or closed, covered or uncovered), other sensory status, and whether studies were controlled or not affect the reproducibility of the study [2]. Third, the different regional parameters (region to whole brain, anterior to posterior, occipital area or cerebellum) and absolute values of activity in rCBF might have influenced results.

In the current study, rCBF correlated with the subscores of attention, anhedonia, and affect. Zemishlany et al also showed a negative correlation between attention and left hyperfrontality [12]. The lower left frontal-temporal base and the right cerebellum had a dominance of flow change in attention subscore in this study. The left anterior hemisphere appears to play an important role in attention, which is similar to this and other studies [12,14]; however, the role of the right hemisphere is still not clear. Zemishlany et al found that the anhedonia subscale was negatively associated with rCBF in the left frontal and posterior regions during the activating condition [12]. In Sagawa et al's study, inferior frontality was associated with negative symptoms such as anhedonia on the Wisconsin Card Sorting Test [14]. It is still unclear whether poor attention or anhedonia, or even

flattened affect, are associated with hypofrontality. Our study showed right hemisphere dominance of flow change in anhedonia. Hypofrontality appeared to be related to anhedonia; however, the involvement of other cerebral regions is controversial. Flattened affect was associated with bilateral frontal change, which is partially compatible with Sabri et al's study in which affective flattening had a negative correlation to frontal, temporal, basal ganglia, and thalamic rCBF ratios on the left side [15]. In the current study, there were no associations between rCBF and SANS in alogia and avolition. These symptoms, which are related to neuroanatomy, require further clarification.

Our results need to be interpreted with caution because of the following limitations. First, medication will influence rCBF [16]. In spite of the non-significance of the correlation between rCBF and neuroleptic dose in the current study, a study with drug-free samples is needed. Second, this study only included a small sample of patients. Third, using the atlas-overlap technique in SPECT imaging to measure rCBF is less accurate than using magnetic resonance imaging co-registration in positron emission tomography.

These results support the positive correlation between frontal lobe dysfunction in rCBF and negative symptoms in patients with schizophrenia. The left anterior hemisphere may play an important role in attention deficit. These negative symptoms, related to neuroanatomy, need further investigation.

Conclusions

Our study supports the hypothesis that frontal lobe dysfunction in schizophrenia is associated with negative symptoms, especially attention, anhedonia, and affect. The left anterior hemisphere plays an important role in attention deficit. The relationships between these negative symptoms and neuroanatomy need further clarification.

Acknowledgments

The authors wish to thank Dr. Yu-Hsuan Chou, Dr. Chew-Cheng Chen, Miss Ching-Lin Chu, and Miss Chin-Yin Hsaio for their statistical, administrative, and editorial assistance in the preparation of this manuscript.

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